Clinical Investigation

Orthostatic Hypotension, Catecholamines, and α-Adrenergic Receptors in Mitral Valve Prolapse

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The reported association of mitral valve prolapse with autonomic dysfunction and neuroendocrine abnormalities is derived from studies of patients selected because of symptoms or specifically referred for investigation. To determine whether such associations occur in nonreferred and unselected women with mitral valve prolapse, we measured blood pressure, heart rate, and norepinephrine response to standing in 13 volunteers with mitral valve prolapse and in 11 control subjects. Platelet α-adrenergic receptor quantity and affinity on standing also were determined in all persons. No significant differences were found between the groups in any of these measurements. Although small subsets of women with mitral valve prolapse may indeed have associated neuroendocrine epiphenomena and autonomic dysfunction, it is probably incorrect to generalize these findings to the vast spectrum of those with mitral valve prolapse.

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Ubiquity in medicine compels attention. Mitral valve prolapse (MVP) has received intense scrutiny, with a consequent generation of substantial quantities of published data; it is probable that some of these may have led to inappropriate conclusions. The concept that the presence of an audible midsystolic click or its echocardiographic correlates always indicates a disease state is an egregious example: thus, a malalignment of the mitral valve and left ventricle may be judged commonly to be associated with a number of important pathophysiologic disorders. For instance, a less-than-scrupulous reader may conclude that MVP has a strong relation with one or more of the following: orthostatic hypotension,[1] panic-anxiety attacks,[2] high α-adrenergic tone,[3,4] β-receptor hypersensitivity,[5] dysautonomia,[6] abnormal catecholamine responses,[7,8] and autonomic dysfunction.[9,10] In fact, these careful studies found abnormalities in MVP patients who were usually symptomatic and who had been specifically referred to cardiac centers for investigation and care. Such selected subjects clearly represent only one part of a vast spectrum of people in whom this anatomic variant exists.

The purpose of our investigation was to determine if postural hypotension, an abnormal heart rate response to standing, excessively elevated catecholamine levels, and altered α-adrenergic receptor quantity and affinity when upright were present to a substantially greater degree in persons with asymptomatic MVP than in controls. Our goal was to study a group of patients with MVP who would reflect, as much as was possible, the actual distribution of that variant in the general population.

Study Population

To obtain an unbiased sample of women with MVP, a one-time notice was sent to medical students, department personnel, and faculty cardiologists asking for volunteers both with and without known, untreated MVP. Exclusions included male sex, age younger than 18 or older than 50, and the use of β-adrenergic blocking or oral contraceptive drugs.

A total of 24 persons were recruited, 13 with MVP and 11 without. Mitral valve prolapse was confirmed on the basis of the unmistakable presence of one or more midsystolic clicks and the typical findings of MVP on the long axis parasternal view of a two-dimensional echocardiographic study. Neither systolic clicks nor late systolic murmurs were heard in the control subjects; a two-dimensional echocardiogram was normal in each. None of the subjects had a chronic illness, took neuroactive medications, smoked, or had consumed caffeine for at least 12 hours before the study.

Protocol

Each person had nothing to eat or drink after midnight; tests were scheduled at 7:30 AM. A heparin-lock needle was inserted into a forearm vein and, to diminish the effect of psychological stress, the subject then rested in a darkened room for 30 minutes. While in this resting supine basal state, the heart rate and forearm blood pressure (BP) were recorded; a venous specimen was also taken to measure the plasma norepinephrine level. Each person then stood quietly for three to five minutes during which the pulse and BP were again recorded and a blood specimen removed for measuring both a plasma norepinephrine level and platelet α-receptor

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ABBREVIATIONS USED IN TEXT
BP = blood pressure
EDTA = ethylenediaminetetraacetate
MVP = mitral valve prolapse

quantity and affinity. A total of 110 ml of blood was removed.

Catecholamines were measured by the standard method of Peuler and Johnson.[11] Laboratory technicians did not know whether plasma specimens came from persons with MVP or from control subjects.

Changes from supine to standing were compared in patients with MVP and in control subjects by the method of analysis of variance. Blood pressures, heart rates, and norepinephrine levels were adjusted for both age and basal (supine) level.[12]

Studies on the specific binding of [^{3}H]yohimbine indicate that the adrenergic receptors on human platelets are exclusively of the α_2 subtype. The specific binding of this ligand to platelet α_2-adrenergic receptors has been suggested to be altered in a variety of disease states.[13] Therefore, the specific binding of yohimbine to platelet membranes was measured in control subjects and in patients with MVP.

Platelet membrane was prepared from the blood specimens as described by Newman and co-workers.[14] About 100 ml of whole blood was collected with an anticoagulant (3.2% citric acid). The blood specimen was centrifuged at 380*g* for ten minutes at 25°C. The resulting platelet-rich plasma was collected and centrifuged again at 16,000*g* for ten minutes at 4°C to sediment the platelets. The pellet was washed three times in cold buffer (0.05 mol per liter tris hydrochloride, 0.15 mol per liter sodium chloride, and 0.02 mol per liter ethylenediaminetetraacetate [EDTA], pH 7.35) and centrifuged again at 16,000*g* for ten minutes at 4°C. Following freezing under liquid nitrogen, then thawing at room temperature, the washed pellet was lysed by homogenization (30 strokes) in 1 ml lysing buffer (0.005 mol per liter tris hydrochloride, 0.005 mol per liter EDTA, pH 7.5) with a motor-driven Teflon-tipped pestle. The final pellet was resuspended in lysing buffer (1 mg per ml) and used immediately. The platelet membrane protein was assayed using the method of Lowry and associates and bovine serum albumin as the standard.[15]

The total yohimbine binding was measured in a final volume of 150 μl containing incubation buffer (0.05 mol per liter tris hydrochloride, 0.005 mol per liter EDTA, pH 7.5), varying concentrations of yohimbine (0.05 to 25 mmol per liter), and freshly prepared platelet membranes. Reactions were initiated by adding membranes and incubating for 20 minutes at 32.5°C. Incubations were terminated by adding 4.0 ml cold incubation buffer. The contents of the tubes were rapidly filtered through Whatman GF/C filters and washed with two 4.0-ml aliquots of incubation buffer. The filters were then dried at 75°C to 90°C and counted in a liquid scintillation counter. Specific binding was defined as yohimbine displaceable by 10^{-5} mol per liter unlabeled yohimbine. All experiments were run in duplicate. Estimates of the maximum number of binding sites (B_{max}) and the apparent dissociation constants (K_d) were determined by Scatchard analysis.[16] In the Scatchard plot the amount of ligand bound is plotted against the ratio of the bound to the free ligand, the B_{max} is the x-intercept, and the K_d is the negative of 1/slope.

Results

There were 13 women with mitral valve prolapse (average age 29.6 years; range, 18 to 40) and 11 control subjects (average age 32.5 years; range, 19 to 49). One person with MVP reported occasional dizziness when upright; otherwise, all were without symptoms.

Standing induced a trivial decline in the systolic blood pressure in both groups; the normal, physiologic increase in the heart rate when upright was not different in MVP patients when compared with controls. Similarly, the elevation in plasma norepinephrine levels, which normally occurs on standing, was not significantly different between the two groups (Table 1).

The 95% confidence limit on differences between persons with mitral valve prolapse and control subjects indicated that the probability that we missed a physiologically important difference (type 2 error) because of an insufficient number of study subjects is negligible (Table 2). Moreover, no differences between the control subjects and the patients with MVP were detected in the measurement of the total number of α-adrenergic receptors (B_{max}) and the dissociation constant reflecting α-adrenergic receptor affinity (K_d) (Table 3).

TABLE 1.—*Orthostatic Changes in Systolic Blood Pressure (BP), Heart Rate, and Plasma Norepinephrine Level**

Variable	Subjects: Control, n=11 Average	Control, n=11 SD	MVP, n=15† Average	MVP, n=15† SD
Supine systolic BP, mm of mercury	103.0	8.9	101.4	9.5
Standing systolic BP, mm of mercury	101.6	10.3	96.6	8.6
Δ in BP	−1.4	8.0	−4.8	8.6
Supine heart rate, beats/min	66.2	9.1	66.8	7.3
Standing heart rate, beats/min	86.8	10.8	87.1	7.2
Δ in heart rate	+20.6	9.6	+21.3	5.9
Supine plasma norepinephrine, nmol/liter	1.276	0.549	1.111	0.342
Standing plasma norepinephrine, nmol/liter	2.736	1.205	2.849	1.022
Δ in plasma norepinephrine	+1.460	1.205	+1.738	0.833

MVP=mitral valve prolapse, SD=standard deviation

*Not adjusted for age and the mean values of the corresponding variable.
†Two subjects were studied twice on 2 separate occasions.

Discussion

In sum, the present data provide no positive evidence of a difference between control subjects and women with mitral valve prolapse in any of the measurements shown in Tables 2 and 3. Although the problem of demonstrating the negative proposition that no differences exist is always more difficult, these data do provide a maximum plausible limit to the variation. For the changes in blood pressure and heart rate, the extreme 95% confidence limits on results between controls and MVP subjects shown in Tables 2 and 3 are such that even if the actual differences were to lie at these limits, they would be physiologically unimportant. For norepinephrine, it is statistically possible, but highly unlikely, that the maximum difference between patients with MVP and controls was 0.721 nmol per liter—about 40%. Thus, although our best estimate is that the variation is much smaller, an increase in norepinephrine cannot be ruled out as a distinguishing factor between controls and MVP subjects.

Thus, we have found no significant differences between our control subjects and those with the clinical and echocardiographic signs of MVP in heart rate, blood pressure, and catecholamine response to standing and in the quantity and affinity of platelet α-adrenergic receptors. Our selection of patients was based solely on the presence or absence of the signs of MVP and not on referral for symptoms or investigation.

Men were finally excluded from the study because our initial request elicited only women volunteers; we subsequently decided to exclude men when only one man volunteered as a control subject. We thought it would be prudent to avoid the potential of sex-determined biologic differences. Whether canvassing for volunteer women working in a hospital or medical school environment closely simulates the universe of MVP is arguable, but it is probably more representative of the general distribution of this disorder in society than would be those patients selected or referred specifically. The data from this group therefore suggest that the vast majority of patients with this anatomic deviation have no abnormal neuroendocrine process.[17]

A number of studies have provided conflicting evidence about the presence or absence of hemodynamic or autonomic nervous system abnormalities in patients with MVP. Such investigations are usually based on an examination of those who have been referred because of specific complaints or for investigation for a particular reason. For instance, Santos and colleagues examined 86 consecutive patients with echocardiographic criteria for MVP and found that 12 of them had substantial orthostatic hypotension.[1] The assumption is that they were referred to the echocardiography laboratory for a specific reason. Venkatesh and co-workers concluded that patients with anxiety neurosis and panic disorders had a higher incidence of MVP because they studied 112 patients with anxiety neurosis from whom 20 were selected for careful study of cardiac findings.[2] Of these, eight were found to have echocardiographic signs of MVP. Their original group of 112 patients had been observed carefully in the psychiatric clinic at the University of Iowa Medical Center. Davies and associates, in an elegant study, found physiologic and pharmacologic β-adrenergic hypersensitivity in nine symptomatic women.[5] Coghlan and co-workers chose 44 patients with MVP from a large population referred to the University of Alabama Medical Center; a number of different signs of autonomic dysfunction were found in this group.[6] Pasternac and colleagues showed that there were increased levels of plasma catecholamines in 15 MVP patients selected for study.[7] Boudoulas and associates investigated 20 symptomatic MVP patients and showed a greater than normal increase in catecholamines with exercise and an increased number of premature ventricular complexes in their patients.[8] Similarly, Gaffney and colleagues concluded that there were hemodynamic abnormalities in 23 women with symptoms "commonly associated with MVP."[9]

Contrary data were provided by Chesler and coinvestigators: they studied 11 consecutive MVP patients, 6 of whom were symptomatic. Although it is unclear whether all 11 had been referred for investigation, there was no evidence of autonomic dysfunction or of neurosis in this group.[18] The presence or absence of specific symptoms could not be correlated with the diagnosis of MVP made by echocardiography, according to a study by Retchin and co-workers.[19] This judgment was made on the basis of a retrospective assessment of medical records, a subsequent correlation with echocardiographic findings, and then telephone interviews of those patients found to be symptomatic.

What are we to make of these disparate results?[17] Clearly, comparisons derived from such studies are hazardous because the characteristics of MVP subjects differ substantially and the selection criteria for investigation of patients vary. Furthermore, serious methodologic problems exist when applying identical experimental designs to patients with vague,

TABLE 2.—*Statistical Evaluation of Changes on Standing for Patients With Mitral Valve Prolapse (MVP) and Controls**

Variable	Decline in Systolic Blood Pressure, mm of mercury	Increase in Heart Rate, beats/min	Increase in Norepinephrine Level, nmol/liter
Overall sample mean, n=34	3.2	20.4	1.601
Standard deviation	±8.4	± 8.0	0.715
MVP mean	3.9	20.1	1.720
Control mean	2.4	20.8	1.477
Difference between MVP and control means	+1.5	− 0.7	+0.242
	NS	NS	NS
Extreme 95% confidence limit on difference	+7.6	+ 4.7	+0.721

NS=not statistically significant

*All data are adjusted for age and for the mean values of the corresponding variable.

TABLE 3.—*Platelet α-Receptor Affinity and Quantity Measurements in Patients With Mitral Valve Prolapse (MVP) and in Control Subjects**

Variable	K_d, mmol/liter†	B_{max}, fmol/mg protein‡
Overall sample mean	5.1	298.0
Standard deviation	±3.0	±135.0
MVP mean	5.6	272.0
Control mean	5.1	316.0
Difference between MVP and control means	±0.5	− 44.0
	NS	NS
Extreme 95% confidence limit on difference	+2.6	−135.0

NS=not statistically significant

*Adjusted for age and mean value of the corresponding variable.
†K_d refers to the dissociation constant reflecting α-adrenergic receptor affinity.
‡B_{max} is the maximum number of binding sites for receptors.

general, and common complaints. The claims generated from each of these studies, therefore, are pertinent only to those patients within the study group; the presence or absence of specific abnormalities in hemodynamics, catecholamines, and an increased incidence of panic or anxiety attacks is entirely dependent on the nature of the individual group studied.

Unfortunately, a commonly held assumption is that mitral valve prolapse is a disease process often associated with serious neuroendocrine abnormalities. This is because the conclusions derived from specific investigations of patients referred or selected are mistakenly generalized to the entire universe of MVP subjects. Boudoulas and associates rightly emphasize the distinction between MVP and what they term "mitral valve prolapse syndrome," which connotes those MVP patients who also show varying degrees of autonomic disturbance.[8] The vast majority of those with MVP clearly do not fall into this latter category.

Mitral valve prolapse is likely an anatomic disorder that only rarely results in serious consequences for patients. Most people with this variant lead a normal life and do not have any important physiologic abnormalities.[17]

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